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In Re Application of:
M. Seul et al.

Serial No. 09/448,420

Filed: 11/22/1999

For: Color-Encoding and in-situ Interrogation of Matrix-Coupled Chemical Compounds

Group Art Unit: 1639

Examiner: P. Ponnaluri

GENERAL INVESTIGATIVE
DIVISION

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Commissioner for Patents
PO Box 1450
Alexandria VA 22313-1450

VIA FAX: (703) 872-9306

Petition for Extension of Time; Notice of Appeal


Dear Sir:

Applicants hereby petition for a one month extension of time, and provide this notice of appeal in the above matter. A Brief on Appeal is attached. Please charge the fee of \$385.00 (\$165.00 for the Notice of Appeal; \$165.00 for the Brief; and \$55.00 for the Petition) associated with this Notice to deposit account no. 502088.

Respectfully submitted,

Dated: 17/11/2003

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Applicants) hereby petitions for any extension of time or for any other grounds needed to make this submission timely and proper. The Commissioner is authorized to charge any additional fees due in this matter or credit any overpayments to Account No. 502088. I hereby certify that, on the date indicated below, this correspondence was sent by fax to the Commissioner for Patents, at (703) 872-9306.

By: [Signature]

Date: 1/13/2003

Status of Amendments.

Amendments after the Final Rejection, filed on November 20, 2003 and December 31, 2003, have not been entered.

Summary of the Invention.

In combinatorial synthesis of a library of compounds, where the library is generated by pooling reagents and then performing a series of reactions, one must be able to trace the reaction sequence for any particular member of the library in order to determine its chemical identity. In the claimed invention, the reactions for synthesizing compounds in a combinatorial library are carried out on solid supports (typically beads). At each step in the reaction, tag(s) are added to the beads such that the tags uniquely identify the reaction sequence and the compound on each of the beads. Decoding of the tags at the end of the process permits determining the chemical identity of the compound on a particular solid support.

After generating the library, one could, if desired, decode the beads, identify the various compounds and then test them to determine which (if any) of the compounds have a property of interest. But to avoid decoding *all* the tags and identifying *all* the compounds in the library, in the claimed invention one first performs an assay on the library which indicates which beads in the library bear a compound having a property of interest, and then decodes the tags on those beads to identify compounds having the property of interest.

The novelty of the claimed invention is that the decoding of the tags is carried out by *in-situ* optical interrogation without isolating the beads being decoded from other beads, and without detaching the tags from the beads. This makes the decoding faster

and more efficient than in the prior art methods where isolation of the "positive" beads and/or detaching the tags is required.

Issues.

Are the claims anticipated under 35 USC 102 by Boyce et al., Dower et al. or Still et al.?
Is the claimed subject matter obvious within the meaning of 35 USC 103(a) over Dower et al. in view of Metzker et al.?

Grouping of Claims.

Claims 173 to 174 are separately patentable from the other claims, 129-166 and 168-171, and should not stand or fall together with the other claims.

Argument.

A. Summary of the Parties' Position

The essential steps described above under the heading "Summary of the Invention" are set forth in the only independent claim, claim 129, as follows (a number of steps and limitations have been omitted for the sake of brevity):

129. A method of *identifying a compound of interest in a library of compounds*, each of said compounds being bound to a solid support and *being produced by a unique reaction series* composed of N reaction steps ...and wherein each compound is produced from components which are independently the same or different, the method comprising:

(c) adding ... one or more tag(s), each tag able to be attached to the solid support and able to be identified by optical interrogation, wherein said one or more tag(s) constitutes a code, which code *is uniquely associated with a compound and a corresponding reaction sequence* and is determined by optical interrogation ...

(f) performing an assay capable of indicating that any compound in the library has a property of interest; and

(g) decoding the code composed of one or more tag(s) to identify the compound associated with the code, wherein the decoding step is carried out without isolating the solid support comprising the compound having the property of interest from other solid supports and without detaching any of the tags(s) from

the solid support comprising the compound having the property of interest, and wherein said decoding step comprises in-situ optical interrogation of the tag(s).

With respect to the 102(b) rejections for anticipation over any of Boyce et al., Dower et al. and Still et al., the Examiner alleges that use of the term "identify" in claim 129 step (g), i.e., "decoding the code composed of one or more tag(s) to *identify* the compound associated with the code," does not distinguish the claimed process from the references cited to support the Section 102 rejections, because in the references, according to the Examiner, compound(s) are "identified" when an assay conducted on a bead-based combinatorial compound library generates a positive assay result. But the decoding step (g) in claim 129 is performed *after* the assay step (f): "performing an assay capable of *indicating that any compound* in the library has a property of interest." Step (f) -- not step (g) -- is the step where, in the words of the Examiner, a *screening* assay is used to "*identify* the compound with a desired biological property." In step (f), beads bearing compounds having a property of interest are indicated (or "identified" in the words of the Examiner) and then in step (g) the positive beads from step (f) are decoded to *identify the compound associated with the code*.

There are several places where the Examiner's comments make clear that she has confused the distinction between step (g), "decoding the code ... to identify the compound" and the assay step (f) of the claims, including this statement in the Final rejection page 9, first paragraph:

And the reference after synthesis is completed, the reaction products *are screened for desired property* by incubating the beads with fluorescently labeled Antibody and the positive beads are identified and separated, which refers to the in-situ optical interrogation of the beads *to identify the compound with desired biological property* of the instant claims.

The terms “in-situ optical interrogation” and “identify” appear only in step (g), and step (f) is “providing an assay” for indicating beads “having the property of interest.” But the Examiner is stating that screening “for desired property ... refers to the in-situ optical interrogation of the beads to identify the compound ...”

The error and illogic of the Examiner’s construction of the terms in the claim is perhaps best illustrated by one of the Examiner’s comments in the Advisory Action mailed 11/10/2003, page 2, last paragraph:

[S]ince the word “identify” does not include determining the structure or sequence of the compound, and the reference identifies the [bead, *sic.*] (by picking up) the bright red beads, which have the compound of interest present. Thus, the reference identified the compound or the bead with the compound by in-situ optical interrogation. If applicants mean “*identifying the compound by in-situ optical interrogation*” applicants are requested to amend the claim to include the limitations. [emphasis added]

Applicants *do* use the term “identify” to mean “identifying the compound by in-situ optical interrogation” in step (g), and that is essentially what step (g) of claim 129 recites: *i.e.*, “decoding the code composed of one or more tag(s) to identify the compound ... wherein said decoding step comprises in-situ optical interrogation of the tag(s).” And, “decoding the code composed of one or more tag(s) to identify the compound ...” in step (g) does *not mean* identify “the compound *or the bead*” as the Examiner implies. The beads bearing compounds having a property of interest are *indicated* in step (f). The specification also clarifies that the “decoding... to identify the compound” is a separate step from “performing an assay capable of indicating that any compound ... has a property of interest” in several places.¹

¹ See *e.g.*, start of the Detailed Description (page 9, lines 16 to 21):

Because one of the same references (Dower et al.) used as the basis for Section 102(b) rejections is the primary reference supporting the Section 103(a) rejections, Applicants' position is that even if one makes the combination in the manner advocated by the Examiner, elements will be missing. Accordingly, there is no prima facie case.

Applicants will now address the specific comments made by the Examiner regarding each rejection and each reference.

B. Analysis of the Section 102(b) Rejections

The Examiner rejected claims 129-151, 160-166, and 168-174 under Section 102(b) as anticipated by Boyce et al. Boyce et al. describe, at column 2, an exemplary combinatorial synthesis, in which members from a group of 10 amino acids are selected to form a set of dipeptides ("AA₁ and AA₂") which are coupled to site V₁ on a compound attached to a bead, producing:

The color coding strategy of the present invention provides a method to place a set of fluorophores - or, more generally, chromophores - on each bead so as to uniquely encode the *chemical identity* of the compound on that bead. Specifically, during each coupling step in the course of DCR combinatorial synthesis, one or more fluorophores are attached to each bead. Decoding is based on the determination of relative abundances of fluorophores on a bead of interest by in-situ optical interrogation. [emphasis added]

In the Summary of the Invention section (page 8, lines 4 to 7):

The identity of the compound anchored to any specific bead is determined in-situ by optically probing individual beads to read the color code, as described herein. This ensures the identification of bead-anchored chemical compounds without the need for physical separation and without the need for off-line chemical analysis. [emphasis added]

And in the Background Section (page 2, lines 27 to 32):

1.2 - Encoded One Bead/One Component Chemical Libraries
One approach to overcoming the serious limitations of standard one bead/one compound chemical libraries is to *encode chemical compound identities*. [emphasis added]

And at page 14, lines 24-25: "BCC and XBCC encode *chemical compound identity* in terms of the relative abundances of fluorophores coupled to each bead." (emphasis added)

10² variants ...[which were] *encoded with eight molecular tags using the binary tagging method described previously....* Finally, the encoded split synthesis procedure above was again employed with eight more tags to complete V₂ by adding AA₃, AA₄ and A_c.” [emphasis added]

Boyce et al. go on to describe that following synthesis of the encoded library:

[A] binding screen was conducted as a solid phase assay in which a sample of the initially colorless bead bound receptor library (1) was treated with a dilute solution of substrate tethered to an intensely colored dye. Binding was detected by simple inspection: receptor library beads which bound to substrate picked up the colored dyes. [col. 2]

The encoded library was then screened for binding with red Leu enkephalin. It was noted that only about 1% of the beads turned bright red, which indicated significant binding to this labeled enkephalin compound. Proceeding on, the authors state:

We picked [about] 50 of these bright red beads and decoded their synthetic histories by gas chromatography to identify AA₁ - AA₄ for those receptors which selectively bound [red Leu enkephalin]. [emphasis added]

Boyce et al., therefore, discuss a two-step process, parallel to steps (f) and (g) of claim 129: (i) a binding screen for positive “bright red” beads, then (ii) *decoding* the history of synthesis to *identify* the sequences of the peptides associated with the positive beads. Boyce et al. even use the term “identify” (see quote above) in the same manner it is used in step (g) of claim 129, *i.e.*, decoding the reaction history to *identify* the compound associated with positive beads. They do not use “identify” in connection with determining which beads appeared bright red (which is the Boyce et al. binding screen step, parallel to step (f)).

At page 4, second from last sentence of the Final Rejection, the Examiner states:

[Boyce et al.] discloses that many beads had developed light orange coloration and few turned bright red (refers to said decoding step comprises in-situ optical interrogation of the instant claims). The reference discloses that bright red beads (refers to other solid supports) and decoded their synthetic history.

The Examiner appears to be saying that the binding screen step in Boyce et al., which resulted in the positive 1% of the beads turning “bright red,” is parallel to the decoding step (g) of claim 129. But Boyce et al. first conducted a binding screen wherein positive beads turned bright red, then “We *picked* [about] 50 of these bright red beads and *decoded their synthetic histories by gas chromatography to identify* AA₁ - AA₄ for those receptors which selectively bound [red Leu enkephalin].” Boyce et al.’s decoding of the beads’ “synthetic histories to identify” the compounds, is parallel to step (g), which states: “decoding the code composed of one or more tag(s) to identify the compound associated with the code...and wherein said decoding step comprises in-situ optical interrogation of the tag(s).” While Applicants do not dispute that Boyce et al. use “in-situ optical interrogation” to determine which beads turned bright red, determining the positive beads is related to the assay step (f) in both the claim and in Boyce et al., and is not part of “decoding... to identify the compounds” in step (g) or in Boyce et al.

Having clarified what the term “identify” in step (g) means (which is the same meaning as in Boyce et al.) it is noted that Boyce et al. do not disclose any of the following three elements (designated as (i), (ii) and (iii) in the claim 1 set forth below) of claim 129:

decoding the code composed of one or more tag(s) to identify the compound associated with the code, wherein the decoding step is carried out [i] without isolating the solid support of interest from other solid supports and [ii] without detaching any of the tags from the solid support of interest and wherein [iii] the decoding step comprises in-situ optical interrogation of the tag(s).

In Boyce et al. the solid support of interest *is isolated* from other solid supports (“We then picked [about] 50 of these bright red beads ...”); the tags *are detached* from the

solid support (“[We] decoded their synthetic histories by gas chromatography ...”) as gas chromatography necessitates volatilizing the tags, thereby “detaching” them from the solid support²; and, because gas chromatography is the method for decoding, the decoding step *does not include* “in-situ optical interrogation of the tag(s).”

The Examiner appears not to dispute that Boyce et al. are missing the above three elements, but feels that the term “identify” does not distinguish step (g) of claim 129, and that if step (g) recited “determining the sequence or structure of the compound” it would not be anticipated by Boyce et al.:

[T]he word “identify” the compound does not include determining the sequence or structure of the compound as in applicants arguments... Thus the reference identified the compound or the bead with the compound by in-situ optical interrogation.³

Of course, Boyce et al. did not perform a step of “*decoding* the code composed of one or more tag(s) to identify the compound associated with the code...and wherein said decoding step comprises *in-situ optical interrogation* of the tag(s).” Boyce et al. *does* identify *the bead* by in-situ optical interrogation, but this is in the binding screen step of Boyce et al., not in the step where Boyce et al. “*decoded [the bright red beads] synthetic histories by gas chromatography to identify AA₁ - AA₄ for those receptors which selectively bound [red Leu enkephalin].*” (emphasis added)

²Or, the gas chromatography analysis of the tags could involve chemical removal (“detachment”) of the tags, followed by gas chromatography analysis. This is made clear in Still et al., US Patent No. 5,565,324, cited and relied on herein by the Examiner (note that Still is the corresponding author of the Boyce et al. reference: thus, the Boyce et al. group was likely following the same method as in this patent). At col. 49, lines 47-56, Still et al. state:

A single, selected bead was placed in a Pyrex capillary tube and washed with DMF The bead was then suspended in DMF ... and the capillary was sealed. The suspended bead was irradiated at 366 nm for 3 hrs *to release the tag alcohols*, and the capillary tube subsequently placed in a sand bath at 90 DEG C for 2 hrs. The tube was opened and bis-trimethylsilyl acetamide (0.1 mL) was added to trimethylsilylate the tag alcohols. After centrifuging for 2 min., *the tag solution above the bead ... was injected directly into an electron capture detection, capillary gas chromatograph for analysis.* [emphasis added]

³ See Advisory Action of 11/10/2003, page 2, para. 4.

The Examiner has also rejected claims 129-138, 142-146, 151, 154 and 159 under Section 102(b) as anticipated by Dower et al., which also discusses, in a process of synthesizing a solid support-based combinatorial library, a two-step process of (i) screening to isolate compounds with a desired property, and (ii) decoding an identifier tag to identify a compound on a particular support:

The present invention provides a general stochastic method for synthesizing libraries of random oligomers. The random oligomers are synthesized on solid supports, or particles, but may be cleaved from these supports to provide a soluble library. The oligomers are composed of a sequence of monomers, the monomers being any member of the set of molecules that can be joined together to form an oligomer or polymer...The library is then *screened* to isolate individual oligomers that *bind to a receptor or possess some desired property*. ...A further embodiment of the invention relates to the use of an identifier tag to *identify* the sequence of monomers in the oligomer. [emphasis added: *see* Dower et al., WO 93/06121, Summary of the Invention, page 3 last line to page 4, line 12]

In the Final Rejection, page 6, last paragraph, discussing Dower et al., the Examiner states: "the instant claimed method [involves] identifying a compound which is attached to a bead from a mixture or pool of beads by in-situ optical interrogation." Again the Examiner's confusion is evident. The term "in-situ optical interrogation" only appears in step (g) of claim 129, which is the step where one is "decoding the code composed of one or more tag(s) to identify the compound associated with the code...and wherein said decoding step comprises in-situ optical interrogation of the tag(s)." Step (g) does not involve or recite beads or pools of beads, and "identifying a compound which is attached to a bead from a mixture or pool of beads...", is parallel to step (f): "performing an assay capable of *indicating* that *any compound* in the library has a property of interest."

Continuing, the Examiner states on page 7, first paragraph of the Final Rejection:

Dower et al. teach after the receptor assay *the positive beads are identified by visual inspection of the fluorescent beads* which refers to the “decoding the code composed of tag to identify the compound associated with the code, ... wherein the decoding step comprises in-situ optical interrogation of the tag” of the instant claims. [emphasis added]

Of course, again, selecting positive beads by visual inspection in Dower et al. does not refer to the “decoding the code composed of tag to identify the compound...” as the Examiner claims. Selecting beads “refers to” step (f) of claim 129, and “decoding...to identify the compound ... wherein the decoding step comprises in-situ optical interrogation” is language from step (g) of claim 129.

Moreover, notwithstanding the contrary implication in the above statement by the Examiner, Dower et al. do not disclose decoding of tags “without isolating the solid support of interest from other solid supports” by “in-situ optical interrogation of the tag,” as in claim 129(g). In Dower et al., beads to be decoded are always isolated. See, Dower et al., e.g., at page 30, lines 5-25. This is true even though in one embodiment of Dower et al.: “the identifier tag may be a set of light-addressable compounds, such as fluorescent or phosphorescent compounds that can be photobleached, which compounds are incorporated into the beads or particles on which the oligomers of the oligomer library are synthesized. ...” See Summary of the Invention, page 4, line 34 to page 5, line 2. But this embodiment is not elaborated on, and specific methods for decoding of these tags are not described. Because the decoding methods which are described in Dower et al. all involve isolation of the beads to be decoded, this leads to the conclusion that these light-addressable tags are also to be decoded in this manner, rather than “without isolating the solid support of interest from other solid supports...” as required in claim 129. In any

event, this required element is certainly not disclosed, either expressly or inherently, in Dower et al.

The Examiner apparently agrees that Dower et al. do not disclose decoding “without isolating the solid support of interest from other solid supports...” as required in claim 129. But the Examiner appears to feel that the term “identify” does not distinguish step (g) of claim 129 from Dower et al., and that if step (g) recited “determining the sequence or structure of the compound” it would not be anticipated by Dower et al.:

Applicants arguments are not persuasive, because ... the phrase ‘identifying the compound by in-situ optical interrogation’ does not include determining the structure or sequence of the compound. If applicants mean that the ‘identifying the compound by in-situ optical interrogation’ includes determining the structure or sequence applicants are requested to amend the claims. [Advisory Action of 11/10/2003, page 3, 3rd paragraph]

Applicants note, in response, that claim 129 step (g) recites that in-situ optical interrogation is used for “decoding ...to *identify the compound*,” and step (c) recites that the “*code is uniquely associated with a compound and a corresponding reaction sequence* and is determined by optical interrogation...” Thus, the “sequence or structure” of the compound will be determined by performing the decoding step (g), which determines “the reaction sequence,” from which the “sequence or structure” naturally flows. In any event, claim 129(g) recites “decoding the code ...to identify the compound associated with the code... wherein said decoding step comprises in-situ optical interrogation of the tag(s),” and step (c) recites that the “*code is uniquely associated with a compound and a corresponding reaction sequence* and is determined by optical interrogation...” and *this is exactly* what Applicants mean.

The Examiner rejected claims 129-138, 142-146, 151, and 155-159 under Section 102(b) as anticipated by Still et al., which is another reference describing synthesis of an encoded particle-displayed combinatorial library, and involves a two-step process of (i) screening the particles for a characteristic of interest, and (ii) decoding encoded tags to determine the reaction history⁴ and identify the compounds:

Encoded combinatorial chemistry is provided, where sequential synthetic schemes are recorded using organic molecules, which define choice of reactant, and stage, as the same or different bit of information. ... Particularly, pluralities of identifiers may be used to provide a binary or higher code, so as to define a plurality of choices with only a few detachable tags. The particles may be screened for a characteristic of interest, particularly binding affinity, where the products may be detached from the particle or retained on the particle. The reaction history of the particles which are positive for the characteristic can be determined by the release of the tags and analysis to define the reaction history of the particle. [Still et al., Abstract]

The Examiner states, with respect to Still et al., that:

The reference discloses that the beads with ligand attached are incubated in an aqueous buffer with monoclonal antibody (for the property to be tested), and the fluorescent beads with attached monoclonal antibody are identified and separated by manually or using FACS from the unstained beads, so long as the tags are retained on the bead under the conditions of sorting. The reference teaches that the fluorescent beads with attached compound are identified from the unstained beads, thus, the reference analyzed the fluorescent data of the beads, to identify the compound of interest in the library. Thus, the reference clearly anticipates the claimed invention. [Final Rejection, page 8, end of first paragraph]

Thus, according to the Examiner, the fluorescent beads with the attached monoclonal antibodies are "identified" and separated from the unstained beads manually or by FACS to "identify" the compound of interest. But this so-called "identification" is not parallel to the decoding step (g) of claim 129, *i.e.* "decoding ... to identify the compound..." It is, rather, parallel to the assay step (f), where compounds "having a property of interest" are

⁴ As noted above, step (c) of claim 129 also recites that tags constitute a code, "which code is uniquely associated with a compound and a corresponding reaction sequence. . ."

indicated. But, in any event, the Examiner's statement is that in Still et al. "the fluorescent beads with attached monoclonal antibody are identified *and separated by manually or using FACS from the unstained beads...*" (Final Rejection, page 8, end of first paragraph). Accordingly, the Examiner has conceded that Still et al. do not disclose that: "the decoding step is carried out without isolating the solid support comprising the compound having the property of interest from other solid supports..." as required in claim 129.

The Examiner also states (pages 8-9) that Applicants arguments regarding patentability over Still et al. "are not persuasive," because:

Still et al. teach that families of compounds can be employed as identifiers, where the number and/or position of a substituent define the choice, and alternatively detectable functionalities such as radioisotopes, fluorescers, halogens can be used. And the reference after synthesis is completed, the reaction products are screened for desired property by incubating the beads with fluorescently labeled Antibody and the positive beads are identified and separated, which refers to the in-situ optical interrogation of the beads to identify the compound with desired biological property of the instant claims.

In contrast to the Examiner's assertion, the portions of Still et al. referring to "incubating beads with fluorescently labeled antibody" are not referencing "in-situ optical interrogation of the beads to identify the compound ..." Rather, where Still et al. refer to incubating of beads with fluorescently labeled antibody, they are referring to screening of the beads for a "property of interest," as in the assay step (f) of claim 129. For example, col. 29, lines 65 to col. 30, line 29, discuss that to "determine the characteristic of interest of the product ... one may provide for an antibody to the receptor, where the antibody is

labeled....”⁵ However, Still et al., at col. 28, lines 59-65. *do* discuss use of fluorescent tags for compound identification:

While fluorescent tags alone may not be sufficient to define a significant number of stages with a significant number of choices ... by providing means for separating the fluorescent tagging molecules based on variations in C or C' one can individually detect the tags by their fluorescence.

It is clear that the decoding of such fluorescent tagging molecules is *not* “carried out without isolating the solid support of interest from other solid supports” and “without detaching any of the tag(s) from the solid support...” as required in claim 129. Still et al. state that one provides “means for separating the fluorescent tagging molecules.”

The Examiner also states on page 9 that:

Applicants' arguments seem to be emphasizing that applicants decoding refers to identifying the structure of the compound, not identifying the positive compound attached to the bead from among other beads.... It is noted that the features upon which applicant relies (i.e., decoding the code to determine the structure of the compound) are not recited in the rejected claim(s).

Prior to the Final Rejection, Applicants' arguments did *not* refer to “identifying the structure of the compound” or “decoding the code to determine the structure of the compound.”⁶ Nevertheless, because claim 129 step (g) recites that in-situ optical interrogation is used for “decoding ...to *identify the compound*,” and step (c) recites that the “code is *uniquely associated with a compound and a corresponding reaction sequence* and is determined by optical interrogation...”Applicants agree that the “sequence or structure” of the compound is readily determined by first performing the

⁵ Still et al. also use the term “identify” in the same manner as in step (g) of claim 129, and not to refer to a screening or assay step (f): “One can determine a characteristic of a product of a synthesis, usually a chemical or biological characteristic by various *screening techniques*, and then *identify the reaction history and thereby the structure of that product*, which has the desired characteristic, by virtue of the tags associated with the product.” See Still et al., US Patent No. 5,565,324, col. 5 lines 59 to 64.

⁶ In response to this assertion and related ones, Applicants did argue this.

decoding step (g), which determines "the reaction sequence," from which the "sequence or structure" naturally flows.

The Examiner also states that:

Still et al. teach after the synthesis is completed, the compounds are screened for desired property either after detachment of the ligand (compound) from the bead or while still attached, which clearly anticipates the claimed invention.

The fact that an assay for the "desired property" (parallel to assay step (f)) can be carried out while the ligand/compound is still attached to the beads, does not change the fact that Still et al. state that the "identifiers contain a cleavable member or moiety which permits detachment of a component which can be readily analyzed." See Col. 3, lines 36-38; Summary of the Invention. The identifiers (or "tags") are used for decoding, parallel to the decoding in step (g) of claim 129. There are no statements in Still et al. that the tag/identifier, which is the encoding means of Still et al., does not get removed from the bead for decoding; they consistently state that it in fact *does* get removed. See, e.g., col. 17, lines 16-18 ("Each selected fluorescent bead is subjected to a means for releasing at least some of the *tags from the bead*."). Thus, for this reason alone, claim 129, which requires decoding "without detaching *any of the tags* from the solid support of interest," is not anticipated by Still et al.

C. Section 103(a) Rejections

The Examiner rejected claims 129-151, 153-166 and 168-174 under Section 103(a) over Dower et al. in view of Metzker et al. The Examiner stated in the Final Rejection, page 11, that:

Metzker et al. teach the fluorescent dyes used in the instant claimed method, and Dower et al. teach a method of synthesis and screening of a library of compounds attached to beads, and the beads are labeled with fluorescent tags....[O]ne cannot

show nonobviousness by attacking references individually where the rejections are based on combinations of references. [citing *In re Keller* and *In re Merck & Co.*]

Applicants demonstrate below that even no matter how the teachings of Dower et al. and Metzker et al. are combined, a *prima facie* case of obviousness is not established.

MPEP Section 2143 provides:

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. *Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.* [emphasis added]

The combined teachings of Dower et al. and Metzker et al. do not “teach or suggest all the claim limitations,” because neither of them, together or separately, teach or suggest that the “decoding step is carried out without isolating the solid support of interest from other solid supports ...” as required in claim 129. Metzker et al. do not in any way relate to use of solid supports or to “decoding the code composed of one or more tag(s) by in-situ optical interrogation of the tag(s) to provide the chemical *identity of the compound associated with the code*,” but only to identification of *classes of polynucleotides* in a gel using certain dyes described therein (see further explanation of Metzker et al. below). The only mention of decoding of identifier tags in Dower et al. relates to the decoding of oligonucleotide sequence tags. Moreover, Dower et al. provide that the identifier tags are decoded by sequencing (page 4, lines 21 to 33). Decoding by sequencing normally involves *isolation* “of the solid support of interest from other solid supports ...”

Although fluorescent tags are mentioned in Dower et al., their decoding is not described. Dower et al. provide that beads to be decoded are always isolated. *See, e.g.*, page 30, lines 5 to 25

The techniques for *selection of individual beads displaying ligands on their surface* are analogous to FACS methods for cloning; mammalian cells ... After washing away unbound or non-specifically bound receptors, one can then use FACS to sort the beads and to *identify and isolate physically individual beads* showing high fluorescence....

Alternatively, affinity adsorption techniques can be employed in conjunction with the libraries of the invention. [Dower et al. then describe an affinity adsorption procedure, where the procedure includes the step that:] Finally, individual beads are *physically separated ...* (emphasis added))

Accordingly, even if Dower et al. and Metzeker et al. are combined, they do not "teach or suggest" the claim limitation that: "decoding step is carried out without isolating the solid support of interest from other solid supports ..." and, accordingly, a *prima facie* case of obviousness has not been established by the combination of these references.

It is further noted that although Dower et al. disclose fluorescent tags, Dower et al. do not mention anywhere, that with respect to any type of the identifier tags discussed (including fluorescent compounds or oligonucleotides or any others) the "decoding step is carried out without isolating the solid support of interest from other solid supports ..." as required in claim 129. The only mention of decoding of any identifier tags in Dower et al. relates to the decoding of oligonucleotide tags. Dower et al. provide that beads to be decoded are always isolated (page 30, lines 5-25, *supra*). Moreover, Dower et al. state that identifier tags are decoded by sequencing (page 4, lines 21 to 33) which normally involves *isolation* "of the solid support of interest from other solid supports ..." Because isolation of the solid support is the only means taught in Dower et al. for decoding, this suggests that the solid supports must be isolated irrespective of whether one is decoding

oligonucleotide tags or fluorescent tags. Accordingly, there is a suggestion in Dower et al. *not* to do what is required in claim 129(g), *i.e.*, the requirement that the "decoding step is carried out *without isolating* the solid support of interest from other solid supports ...". As such, Dower et al. teach away from the claimed invention.

Turning to Metzker et al., they only describe the use of modified versions of a new class of dyes, *i.e.*, BODIPY.RTM. fluorophores, for DNA sequencing by the chain termination method of DNA sequencing. As set forth in their claim 1, Metzker et al. relates to a method for distinguishing among four types of polynucleotides, each distinguished by having different 3'-terminal dideoxynucleotides, based on attaching one of four different fluorophores to each of the four different types of polynucleotides and running them in an electrophoresis gel, or by attaching the same fluorophore to all four different types of polynucleotides, but separating each type of polynucleotide by running it in a separate electrophoretic lane from the others. Metzker et al. also describe use of these dyes in internal labelling of polynucleotides by enzymatic incorporation of fluorescently-labeled ribonucleotides or deoxyribonucleotides.

Metzker et al. do not in any way suggest or motivate one to make the claimed invention, as these dyes and methods are not used for "decoding the code composed of one or more tag(s) to identify the compound ..." as in claim 129. Metzker et al.'s method only allows determination of *classes of polynucleotides* (*not* "decoding... to identify the [polynucleotides]" as in claim 129) which have the same 3'-terminal dideoxynucleotides (see claims 1-6 of Metzker et al.), or *classes* which contain the same ribonucleotides (claim 7 of Metzker et al.) or *classes* which contain the same deoxynucleotides (claim 12 of Metzker et al.). Combining Dower et al. with Metzker et al. does not, therefore, affect

the teaching away from the invention in Dower et al. Accordingly, there is no motivation to modify Dower et al. to provide "decoding ... to identify the compound" without "isolation of the solid supports," as no reference discloses or suggests such modification, and for this further reason, there is no *prima facie* case of obviousness. See MPEP 2143, *supra*.

D. Separate Consideration of the Rejection of Claims 172-174 under Section 103(a)

Applicants requested that claims 172-174 be considered separately. The Examiner has included them in the rejection under Section 103(a), over Dower et al. in view of Metzker et al., but has not indicated where in these references the following limitations (*italicized below*) appear:

172. The method of claim 171, wherein the planar array of beads is formed adjacent to *the planar walls of a sandwich flow cell* and controlled by *light-controlled electrokinetic means*.

173. The method of claim 170, wherein spectral fluorescence data are collected for the bead array *by initially forming a spatially encoded array of beads at an interface between an electrode and an electrolyte solution*, comprising the following steps:

- (a) providing an electrode and an electrolyte solution;
- (b) providing multiple types of beads, each type being stored in accordance with chemically or physically distinguishable bead characteristics *in one of a plurality of reservoirs, each reservoir containing a plurality of like-type beads suspended in said electrolyte solution*;
- (c) *providing said reservoirs in the form of an mxn grid arrangement*;
- (d) *patterning said electrode to define mxn compartments corresponding to said mxn grid of reservoirs*;
- (e) *depositing mxn droplets from said mxn reservoirs onto said corresponding mxn compartments, each said droplet originating from one of said reservoirs and remaining confined to one of said mxn compartments and each said droplet containing at least one bead*;
- (f) *positioning a top electrode above said droplets so as to simultaneously contact each said droplet*;
- (g) *generating an electric field between said top electrode and said mxn droplets*;

- (h) *using said electric field to form a bead array in each said mxn compartments, each said bead array remaining spatially confined to one of said mxn droplets;*
- (i) *illuminating said mxn compartments on said patterned electrode with a predetermined light pattern to maintain the position of said bead arrays in accordance with said predetermined light pattern and the pattern of mxn compartments and*
- (j) *positioning said top electrode closer to said electrode thereby fusing said mxn droplets into a continuous liquid phase, while maintaining each of said mxn bead arrays in one of the corresponding mxn compartments.*

174. The method of claim 173, wherein said *compartments are hydrophilic and the remainder of said electrode surface is hydrophobic.*

The Examiner is apparently relying on Metzker et al. for disclosure or teaching of the italicized elements above. However, Metzker et al. relates to novel fluorophores for use in electrophoresis, which involves tagging various polynucleotides with the fluorophores and running them in the electrophoresis gel. Electrophoresis, as in Metzker et al., does not, however, involve: forming “planar array of beads is formed adjacent to the planar walls of a sandwich flow cell and controlled by light-controlled electrokinetic means” as required in claim 172; Metzker et al. does not disclose: “initially forming a spatially encoded array of beads at an interface between an electrode and an electrolyte solution,” as well as all the italicized limitations above in claim 173, and including, most ostensibly, “illuminating said *mxn* compartments on said patterned electrode with a predetermined light pattern to maintain the position of said bead arrays in accordance with said predetermined light pattern and the pattern of *mxn* compartments”; Metzker et al. does not disclose the limitation in claim 174 that “compartments are hydrophilic and the remainder of said electrode surface is hydrophobic.” Due to the absence of a teaching, disclosure or suggestion of these elements in Metzker et al. or any other cited reference,

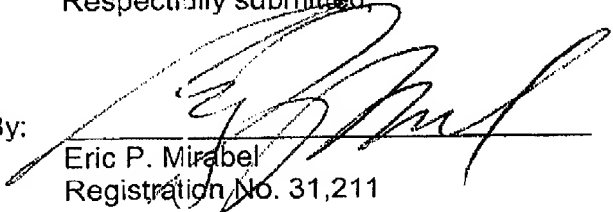
there is no prima facie case of obviousness with respect to claims 172-174 for these additional reasons.

Accordingly, it is clear that the rejections under Section 102 should be reversed, due to the absence of required claim elements in the prior art, and the rejections under Section 103(a) should also be reversed, because a *prima facie* case of obviousness has not been established.

Respectfully submitted,

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